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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

HM22/0404

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ART UNIT	PAPER NUMBER
1644	25

DATE MAILED: 04/04/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 1/31/00

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-9, 11-45 is/are pending in the application.
Of the above, claim(s) 16, 17, 21, 22, 25, 26, 29-45 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-9, ~~10~~ 11-15, 18-20, 23-24, 27-28 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 22
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1996-404-496/40517

Part III DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C.121:

Group I. Claims 1-15,18-20, 23, 24, 27, and 28, drawn to humanized immunoglobulin having binding specificity for $\alpha 4\beta 7$ integrin, classified in Class 530, subclass 387.3.

Group II. Claims 16-17, 21, 22, 25, 26, and 29-40, drawn to nucleic acid, vector, and host cells, classified in Class 536, subclass 23.53, and Class 435, subclasses 320.1, 69.1 and 252.3.

Group III. Claims 41-45, drawn to a method of treatment, classified in Class 424, subclass 133.1.

2. The inventions of Groups I and II represent distinct products having different structure and function. They are unrelated in operation and one does not require the other for ultimate use. The inventions of these two groups have biochemically distinctive and unrelated structure and are biologically distinct and unrelated functionally. They are patentable over one another.

3. Inventions as grouped in Groups I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can

be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. 806.05 (h)). In the instant case, the product can be used to purify antigen.

4. Because these inventions are distinct for the reasons given above and have acquired a separate status as shown by their different classification and divergent fields of search, restriction for examination purposes as indicated is proper.

5. During a telephone conversation with David Brook on June 2, 1997, a provisional election was made with traverse to prosecute the invention of Group I, Claims 1-15, 18-20, 23, 24, 27, and 28. Affirmation of this election must be made by applicant in responding to this Office action. Claims 16, 17, 21, 22, 25, 26, and 29-45 are held to be withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142 (b), as being drawn to a non-elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

7. Claims 1-15, 18-20, 23, 24, 27, and 28 are currently under examination.

Claim Rejections - 35 USC § 112

8. Claims 1-7, 23, 24, 27, and 28 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The specification does not enable a person of skill in the art to determine the exact amino acid residues to select for the claimed "at least a portion of " or "at least a functional portion of" of the recited immunoglobulin molecules and particular sequences. Thus, the specification does not teach how to make functional immunoglobulin comprising portions of the particular sequences disclosed in the specification or a teaching of how to use them commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the peptides that reflect portions of immunoglobulin molecules. There is insufficient guidance to direct a person of skill in the art to know, for example, which portions when minimally sized portions are considered, if administered, would result in binding. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which sequences are required to retain similar activity and function requires a detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein are well outside the realm of routine experimentation. Therefore, it is unpredictable whether any of the "portions" to which the claims are drawn would be active in the instant protein. The true fact of the state of the art in peptide chemistry is expressed succinctly by Rudinger [Peptide Hormones, Parsons (Ed.), University Park Press, Baltimore, MD, Pp. 1-7]: "The

significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (see the Conclusions in particular).

From the discussion above, it is clear that the predictability of changes to an amino acid sequence is practically nil as far as biological activities are concerned. The specification fails to provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in a manner reasonably correlated with the broad scope of the claims including any number of fragments or portions of any size. *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Without such guidance, the changes which can be made in the protein structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

In view of the lack of predictability of the art to which the invention pertains and the limited working examples, the state of the prior art, the lack of guidance in the specification and the breadth of the claims, it would take undue experimentation to practice the invention as broadly claimed and this is not sanctioned by the statute.

9. Claims 1-7, 23, 24, 27, and 28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-7 are indefinite for reciting "portion of" because the relevant portions have not been identified.

B. Claims 1-7 are indefinite for reciting "at least a portion of" because it is unclear how much of the peptide is required.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-15, 18-20, 23, 24, 27, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Queen *et al.* [U. S. Patent 5,530,101 (102(e) Date: Dec 28 1988)] in view of Lazarovits *et al.* [J. Immunol. 151 (11): 6482-6489 (Dec 1993)].

Queen *et al.* teach humanized immunoglobulin (Ig) chains having one or more complementarity determining regions (CDRs) from a donor Ig and a framework region from a human Ig. Queen *et al.* teach that a humanized light and heavy chain can be used to form a complete humanized Ig or antibody, having two light/heavy chain pairs, with or without partial or full-length human constant regions. Queen *et al.* teach that to form the humanized variable region, amino acids in the human acceptor sequence

will be replaced by the corresponding amino acids from the donor sequence if they are in a CDR (Column 2, Lines 35-67, in particular). Queen *et al.* teach that the extent of the framework region and CDR's have been precisely defined by Kabat *et al.* (Column 11, Lines 38-42, in particular). Queen *et al.* further teach that other substitutions are required in the human framework in order for the antibody to "be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen" (Column 3, Lines 33-36, in particular). Queen further outlines other categories wherein amino acids in the human acceptor sequence are replaced by the corresponding amino acids from the donor sequence (Column 3, Lines 1-31, in particular). Queen *et al.* teach that in some cases, it may be considered preferable to use light and heavy chains from the same human antibody as acceptor sequences to be sure the humanized light and heavy chains will make favorable contacts with each other, *e.g.*,Eu, Lay, Pom (Column 13, Lines 39-56, in particular). Queen *et al.* teach that typically one of the 3-5 most homologous heavy chain variable region sequences in a representative collection of at least about 10 to 20 distinct heavy chains will be chosen as acceptor to provide the heavy chain framework, and similarly for the light chain and that the selected acceptor immunoglobulin chain will most preferably have at least about 65% homology in the framework region to the donor immunoglobulin (Column 13, Lines 32-40, in particular).

Queen *et al.* teach humanized antibodies having affinity for a receptor different from $\alpha 4\beta 7$, the receptor for fibronectin and vascular cell adhesion molecule-1. For example, Queen *et al.* teach humanized anti-Tac (IL-2R) (Columns 45-49, in particular). Queen *et al.* teach that humanized antibodies have at least three potential advantages over mouse or in some cases chimeric antibodies for use in human therapy: (1) because the effector portion is human, they interact better with other parts of the human immune system, (2) they are less immunogenic, (3) they have a half-life more similar to naturally occurring human antibodies allowing smaller and less frequent doses to be

given (Column 16, Lines 6-26, in particular). Queen *et al.* teach that humanized Igs can be more economically produced (Column 68, Lines 12-14, in particular).

Queen *et al.* do not teach humanized antibodies having binding specificity for $\alpha 4\beta 7$ integrin, specifically "humanized" Act-1 mAb. However, Lazarovits *et al.* teach Act-1 mAb and that the antigen recognized by Act-1 is $\alpha 4\beta 7$, the receptor for fibronectin and vascular cell adhesion molecule-1. Lazarovits *et al.* teach that data on T cells binding to synovium indicate that interference with $\alpha 4\beta 7$ may be beneficial in the immunotherapy of rheumatoid arthritis (Page 6487, Last paragraph, in particular). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the humanized antibodies of Queen *et al.* for the Act-1 mAb taught by Lazarovits *et al.*. Queen *et al.* teach that once an antibody (nonhuman) is chosen, following their criteria, *i.e.*, choosing the human framework, choosing which particular amino acids should be donor or acceptor, and following their reasoning for making changes, any antibody can be humanized. Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to be motivated to use the methods of Queen and the mAb taught by Lazarovits *et al.* to make humanized Act-1 antibody including fragments, multimers, fusion proteins and conjugates, with the expectation that an antibody would be successfully obtained and useful for therapeutic treatments, for diagnostic assays, and for purifying ligand. One would have been motivated to do so because of Queen's teachings of the advantages of humanizing antibodies and the teachings of Lazarovits *et al.* indicating its importance. Based on the teachings of the references, one of ordinary skill in the art would have a reasonable expectation of success in producing the claimed antibodies. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Rabin, Ph.D. whose telephone number is (703) 305-6811. The examiner can normally be reached on Monday through Friday from 9:30 AM to 6:00 PM.

13. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The FAX number for this Group is (703) 305-7939. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Evelyn Rabin

Evelyn Rabin, Ph.D.

June 4, 1997

FRANK C. EISENSCHENK
PRIMARY EXAMINER
GROUP 1800

6/4/97